

- perspectives from program directors. *Academ Emerg Med.* 2012;19:1073-78.
4. Emergency department targeted ultrasound interest group. Canadian Association of Emergency Physicians. Emergency department targeted ultrasound: 2006 update. *CJEM.* 2006;8:170-1.
  5. Canadian Association of Radiologists. CAR position paper: portable ultrasound in emergency departments. September 2006.
  6. Choi D. Emergency ultrasound: A stethoscope extension? *CJEM* 2008; 10(6):579-80.
  7. Campana B. The ultrasound controversy. *CJEM.* 1999;1(2):122.
  8. McPhee D. A radiologist's perspective. *CJEM.* 1999;1(2):123-124.
  9. Blaivas M, Pawl R. Analysis of lawsuits filed against emergency physicians for point-of-care emergency ultrasound examination performance and interpretation over a 20-year period. *Am J Emerg Med.* 2012;30(2).
  10. Welch, S. Bedside ultrasound: a wrong turn somewhere? *Emergency Medicine News.* March 2010.
  11. Woo MY, Nussbaum C, Lee AC. Emergency medicine ultrasonography: national survey of family medicine-emergency medicine program directors. *Can Fam Physician* 2009;55:1010-1.

## Hepatitis B: A Concise Review

Harley T. Syyong<sup>a</sup>, BSc, PhD; Eric M. Yoshida<sup>b</sup>, MD, FRCPC

<sup>a</sup>Vancouver Fraser Medical Program 2016, UBC Faculty of Medicine, Vancouver, BC

<sup>b</sup>Division of Gastroenterology, Vancouver General Hospital, University of British Columbia, Vancouver, BC

### ABSTRACT

Since the introduction of Hepatitis B preventative measures including the vaccine, the worldwide prevalence of Hepatitis B viral (HBV) infection has fallen. Despite this, chronic infection still remains a major global health problem, with more than 350 million people chronically infected. Chronic infection leaves those affected at risk of hepatic decompensation, cirrhosis, and hepatocellular carcinoma. In developed countries, the burden of disease is greatest among marginalized populations and immigrants from regions where HBV is endemic, making chronic hepatitis B an important, but clinically silent public health issue. The approval of the first potent oral antiviral agent in 1998 has revolutionized the management of hepatitis B, and current treatments such as conventional and Pegylated Interferon alpha as well as nucleoside and nucleotide analogues are widely used to suppress virus replication, reduce hepatitis activity, and halt disease progression. Nevertheless, because those most affected rarely seek medical attention, these treatments often fail to reach those who most need them. Fear of stigmatization and insufficient knowledge of HBV are important barriers to screening and treatment. As the immigrant population increases in Canada, medical students should be aware of opportunities for education, screening, prevention, and treatment of chronic hepatitis B to increase awareness and limit the spread of the disease.

**KEYWORDS:** *chronic hepatitis B, HBV, cirrhosis, hepatocellular carcinoma*

### INTRODUCTION

**H**epatitis B is a serious global health problem, and despite the availability of a highly effective vaccine, approximately 350 million people are chronically infected worldwide. Approximately 0.5 to 1.2 million people die yearly due to Hepatitis B virus (HBV)-associated liver pathologies such as cirrhosis and hepatocellular carcinoma (HCC).<sup>1-3</sup> In Canada, between 240,000 to 600,000 people, up to 70% of them immigrants, are thought to have chronic HBV infection.<sup>4-6</sup>

#### Natural history of acute and chronic hepatitis B infection

HBV is a partially double-stranded, enveloped DNA virus that infects hepatocytes. Transmission of HBV can occur vertically from infected mother to child. HBV can also be transmitted horizontally through sexual contact or paraenterally through IV drug use, sharps injury,

or contaminated blood products. After infection of hepatocytes, the viral genome is delivered to the nucleus and converted to covalently-closed circular DNA (cccDNA). This cccDNA serves as a template for the transcription of key markers of HBV infection, including the HBV surface antigen (HBsAg) and e-antigen (HBeAg).<sup>7</sup> HBV infection is not directly cytopathic, except under specific conditions of significant immunosuppression—such as chemotherapy or post-transplant immunosuppressive medications—but leads to a wide spectrum of liver disease from acute to chronic viral hepatitis. These outcomes are a result of the hosts' immune response attempting to control the infection, specifically in the case of cirrhosis. The serum level of HBV-DNA is associated with cirrhosis and HCC development in a dose-dependent manner, suggesting that HBV replication, with subsequent immune-mediated liver injury, is the primary driving force for liver disease progression, while cirrhosis, regardless of its etiology, is itself a strong risk factor for HCC.<sup>8-9</sup>

HBV infection can be either acute or chronic. In an acute infection, the initial incubation phase lasts 2-6 weeks, and the

#### Correspondence

Harley Syyong, harley.syyong@alumni.ubc.ca.

immune system will usually determine the outcome of the infection, with the severity of hepatocyte injury reflecting the vigor of the immune response.<sup>10</sup> After viral DNA levels decline, a cytolytic immune response with hepatocyte apoptosis and necrosis ensues, coincident with the onset of clinical hepatitis. In acute HBV infection, 30% of adults present with jaundice and acute hepatitis, and 0.1-0.5% will develop fulminant liver failure.<sup>11</sup> In 90-97.5% of cases, the acute hepatitis resolves and the immune system clears the HBV.<sup>12-13</sup> Serologically (see Table 1), the successful resolution of acute HBV is characterized by seroconversion from HBsAg positivity, indicating active HBV infection, to anti-HBs positivity, implying immunity to future HBV infections. At this point, liver enzyme levels normalize and blood tests for HBV DNA become negative.

The persistence of HBsAg (see Table 1) greater than six months from its first detection denotes chronic HBV infection.<sup>14</sup> The likelihood of developing Chronic Hepatitis B (CHB) varies inversely with the age at which the infection is acquired; in adults who suffer acute HBV infection, the risk is less than 5%, while newborns who acquire HBV during birth have a 90% risk of developing CHB.<sup>15-17</sup>

The natural history of untreated chronic HBV infection can be divided into four states: immune tolerant, immune clearance, inactive phase, and re-activation phase; however, not all of those who are chronically infected will develop all four phases, or develop them sequentially.<sup>18</sup> The immune tolerant phase is mostly seen in patients infected at birth and it may last for decades. It is characterized by positivity for serum HBeAg, high levels of HBV DNA, normal alanine aminotransferase (ALT) levels, and a near normal histological profile on liver biopsy. Later in life, an immunologic response develops, accompanied by chronic hepatitis and progressive liver damage.

The immune clearance phase begins when the host mounts an immune response to the HBV-infected hepatocytes, which reduces HBV replication and begins to clear HBeAg and HBsAg.<sup>19</sup> HBeAg seroconversion to the HBeAg-negative status is key, because a mutation in the pre-core or core promoter region of the HBV genome prevents the production of HBeAg, resulting in the development of anti-HBe antibodies. This is associated with a three to four log decrease in HBV viral load, resolution of liver inflammation, and improved clinical outcomes.<sup>20</sup>

Following HBeAg seroconversion is the inactive phase, characterized by minimal HBV replication and low or undetectable HBV DNA. HBeAg is negative, but HBsAg remains positive, and it is important to appreciate that cirrhosis may already have occurred. Ten percent of patients in this phase will reactivate to HBeAg-positive CHB, while 10-20% will reactivate to HBeAg-negative CHB.<sup>21</sup> The re-activation phase is characterized by flares of serum ALT levels and HBV viral load, with further progression of chronic inflammation and fibrosis. In the setting of established cirrhosis, the re-activation phase can be life-threatening, and it is important for clinicians to appreciate that re-activation can be precipitated by immunosuppressive medications including oncologic chemotherapy, and immunomodulatory drugs for organ transplantation, inflammatory bowel disease, and rheumatoid arthritis.<sup>22-23</sup>

**Table 1.** Interpreting Hepatitis B Serology.

Serologic Test	Interpretation
HBsAg	Hepatitis B surface antigen - Always means that patient has active infection
Anti-HBsAg	In the absence of HBsAg, implies clearance of Hepatitis B virus (HBV, after acute infection), or immunization against HBV. Titres > 10 IU/L are considered protective against future HBV infection
Anti-HBc	Antibody against HBV core antigen. There is no test for HBV "core antigen". A positive test means that the patient has been infected with hepatitis B in the past. This test does not distinguish between a previous cleared infection or active carrier state
HBeAg	Hepatitis B "E" antigen - Implies an actively replicating state of HBV infection and is associated with high viral loads
Anti-HBeAg	In the absence of HBeAg, this implies "E antigen seroconversion." Typically means a decrease in HBV viral load from previous and less replicative activity. Anti-HBeAg chronic hepatitis (or 'e antigen negative 'CHB') is still associated with inflammation and can result in on-going fibrosis


**Chronic Hepatitis B in British Columbia**

Canada as a nation, but in particular the province of British Columbia, is faced with challenges posed by immigration. Between 1981 and 2006, 90% of immigrants came from countries where HBV is endemic, and the HBV-infected population in Canada is estimated to increase by approximately 1000 per year through immigration.<sup>5</sup> In BC, the introduction of universal HBV immunization in infants and Grade six students has almost completely eliminated acute hepatitis B among adolescents;<sup>39-40</sup> however, serological screening of CHB is not routinely conducted in immigrants entering Canada or by physicians. In contrast, HBV screening recommendations in the USA have been revised to include people who are born in geographical areas with HBsAg prevalence of greater than 2%.<sup>41</sup> Furthermore, universal HBV vaccination will not have a major effect on the prevalence of HBV in immigrants coming into Canada due to the late introduction of vaccination in countries where HBV is endemic.

In the immigrant population, major barriers to the effective management of CHB include cultural, socioeconomic/accessibility issues, as well as a lack of knowledge of HBV that correlates strongly with education level, English fluency, and household income.<sup>42-43</sup> Yet the most significant barrier is the fear of stigmatization associated with being identified as one who is affected with a chronic disease; only one-third of surveyed immigrant patients were willing to share their CHB status with family and friends.<sup>44</sup> In particular, CHB patients from China were more likely to be fearful of discrimination.<sup>45</sup> Furthermore, knowledge deficits regarding modes of transmission of HBV or consequences of CHB are prevalent in the immigrant population. Over 60% of Chinese and Southeast Asian Canadians in Vancouver were unaware that HBV could cause HCC or cirrhosis, while 50% of survey respondents from another study erroneously believed HBV could be spread by food or eating utensils.<sup>46-47</sup> Such studies demonstrate the importance

of increasing awareness and dispelling misconceptions about CHB among the immigrant population, as well as addressing the issue of stigmatization. It is also important that medical students, residents, and health professionals are aware of HBV; a survey conducted among family medicine residents across Canada revealed gaps in their knowledge of primary prevention, disease recognition, and managing cirrhosis as part of the treatment of CHB, suggesting that opportunities to prevent potentially life-threatening complications are being missed.<sup>48</sup>

## CONCLUSION

CHB is a serious but manageable disease which can be treated effectively to delay or prevent progression to liver diseases such as cirrhosis and HCC. Although HBV cannot be completely eradicated by current treatments, a reduction in HBV DNA to undetectable levels is possible, and the outlook for new treatments is positive. As more immigrants from HBV endemic countries settle in Canada, particularly in British Columbia, opportunities for education about screening, treatment, and prevention of HBV should be identified. In particular, medical students and health professionals should be aware of the potential barriers to treatment of CHB in immigrants, including the fear of stigmatization of patients who have been identified with CHB. 

## REFERENCES

- Custer B, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis B virus. *J Clin Gastroenterol*. 2004;38(10):S158-168.
- Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepatol*. 2004;11(2):97-107.
- Block TM, Guo H, Guo JT. Molecular virology of hepatitis B virus for clinicians. *Clin Liver Dis*. 2007;11(4):685-706.
- Zhang J, Zou S, Giulivi A. Epidemiology of hepatitis B in Canada. *Can J Infect Dis*. 2001;12(6):345-50.
- Leber A, Sherman M. Estimation of immigration related chronic hepatitis B infection and hepatocellular carcinoma development in Canada from 1981-2006. *Can J Gastroenterol*. 2008;23(Suppl A):22.
- Sherman M, Bain V, Villeneuve JP, Myers RP, Cooper C, Martin S, et al. The management of chronic viral hepatitis: A Canadian Consensus Conference 2004. *Can J Gastroenterol*. 2004;18(12):715-28.
- Summers J, Mason WS. Replication of the genome of a hepatitis B-like virus by reverse transcription of an RNA intermediate. *Cell*. 1982;29(2):403-15.
- Liaw YF. Hepatitis B virus replication and liver disease progression: the impact of antiviral therapy. *Antiviral Ther*. 2006;11(6):669-79.
- Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127(5):S35-50.
- Lee WM. Hepatitis B virus infection. *N Engl J Med*. 1997;337(24):1733-45.
- Kao HJ. Diagnosis of hepatitis B virus infection through serological and virological markers. *Expert Rev Gastroenterol Hepatol*. 2008;2(4):553-62.
- McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis*. 1985;151(4):599-603.
- Kuruuzum Z, Ozgenc O, Havuk A, Coşkuner A, Ari A, Celenkoğlu N. Rate of chronicity and time of disappearance of HBsAg following acute hepatitis B. *Hepatogastroenterology*. 2009;56(90):466-9.
- Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet*. 1983;2(8359):1099-102.
- Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmunes W, et al. Incidence of hepatitis B virus infections in preschool children in Taiwan. *J Infect Dis*. 1982;146(2):198-204.
- Coursaget P, Yvonne B, Chotard J, Vincelot P, Sarr M, Diouf C, et al. Age- and sex-related study of hepatitis B virus chronic carrier state in infants from an endemic area (Senegal). *J Med Virol*. 1987;22(1):1-5.
- Fattovich G. Natural history and prognosis of hepatitis B. *Semin Liver Dis*. 2003;23(1):47-58.
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology*. 2006;131(6):1743-51.
- Giacchino R, Cappelli B. Treatment of viral hepatitis B in children. *Expert Opin Pharmacother*. 2010;11(6):889-903.
- Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology*. 2002;35(6):1522-7.
- McMahon BJ, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska natives chronically infected with hepatitis B virus. *Ann Intern Med*. 2001;135(9):759-68.
- Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis*. 2006;65(8):983-9.
- Manzano-Alonso ML, Castellano-Tortajada G. Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy. *World J Gastroenterol*. 2011;17(12):1531-7.
- Mommeja-Marin H, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology*. 2003;37(6):1309-19.
- Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEAled. *J Gastroenterol Hepatol*. 2011;26(4):628-38.
- Chen CF, Lee WC, Yang HI, Chang HC, Jen CL, Iloeje UH, et al. Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. *Gastroenterology*. 2011;141(4):1240-8.
- Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet*. 2005;365(9454):123-9.
- Buster EH, Hansen BE, Lau GK, Piratvisuth T, Zeuzem S, Steyerberg EW, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferonalfa. *Gastroenterology*. 2009;137(6):2002-9.
- Buster EH, Schalm SW, Janssen HL. Peginterferon for the treatment of chronic hepatitis B in the era of nucleos(t)ide analogues. *Best Pract Res Clin Gastroenterol*. 2008;22(6):1093-108.
- Scaglione SJ, Lok AS. Effectiveness of hepatitis B treatment in clinical practice. *Gastroenterology*. 2012;142(6):1360-8.
- Hadziyannis SJ, Papatheodoridis GV. Hepatitis B e antigen negative chronic hepatitis B: natural history and treatment. *Semin Liver Dis*. 2006;26(2):130-41.
- Seto WK, Lai CL, Fung J, Wong DK, Yuen JC, Hung IF, et al. Significance of HBV DNA levels at 12 weeks of telbivudine treatment and the 3 years treatment outcome. *J Hepatol*. 2011;55(3):522-8.
- Pol S, Lampertico P. First-line treatment of chronic hepatitis B with entecavir or tenofovir in 'real-life' settings: from clinical trials to clinical practice. *J Viral Hepat*. 2012;19(6):377-86.
- Wu GY, Zheng XJ, Yin CC, Jiang D, Zhu L, Liu Y, et al. Inhibition of hepatitis B virus replication by Bay 41-4109 and its association with nucleocapsid disassembly. *J Chemother*. 2008;20(4):458-67.
- Petersen J, Dandri M, Mier W, Lütgehetmann M, Volz T, von Weizsäcker F, et al. Prevention of hepatitis B virus infection in vivo by entry inhibitors derived from the large envelope protein. *Nat Biotechnol*. 2008;26(3):335-41.
- Lanford RE, Guerra B, Chavez D, Giavedoni L, Hodara VL, Brasky KM, et al. GS-9620, an oral agonist of toll-like receptor-7, induces prolonged suppression of hepatitis B virus in chronically infected chimpanzees. *Gastroenterology*. 2013;144(7):1508-17.
- Lopatin U, Wolfgang G, Tumas D, Frey CR, Ohmsted C, Hesselgesser J, et al. Safety, pharmacokinetics and pharmacodynamics of GS-9620, an oral Toll-like receptor 7 agonist. *Antivir Ther*. 2013;18(3):409-18.
- Cai D, Mills C, Yu W, Yan R, Aldrich C, Saputelli J, et al. Identification of the Disubstituted Sulfonamide Compounds as Specific Inhibitors of Hepatitis B Virus Covalently Closed Circular DNA Formation. *Antimicrob Agents Chemother*. 2012;56(8):4277-88.
- Dobson S, Scheifele D, Bell A. Assessment of a universal, school-based hepatitis B vaccination program. *JAMA*. 1995;274(15):1209-13.
- Patrick DM, Bigham M, Ng H, White R, Tweed A, Skowronski DM. Elimination of acute hepatitis B among adolescents after one decade of an immunization program targeting Grade 6 students. *Pediatr Infect Dis J*. 2003;22(10):874-7.
- Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep*. 2008;57(RR-8):1-20.
- Thompson MJ, Taylor VM, Yasui Y, Hislop TG, Jackson JC, Kuniyuki A, et al. Hepatitis B knowledge and practices among Chinese Canadian women in Vancouver, British Columbia. *Can J Public Health*. 2003;94(4):281-6.

43. Li D, Tang T, Patterson M, Ho M, Heathcote J, Shah H. The impact of hepatitis B knowledge and stigma on screening in Canadian Chinese persons. *Can J Gastroenterol*. 2012;26(9):597-602.
44. Wu H, Yim C, Chan A, Ho M, Heathcote J. Sociocultural factors that potentially affect the institution of prevention and treatment strategies for prevention of hepatitis B in Chinese Canadians. *Can J Gastroenterol*. 2009;23(1):31-6.
45. Mohamed R, Desmond P, Suh DJ, Amarapurkar D, Gane E, Guangbi Y, et al. Practical difficulties in the management of hepatitis B in the Asia-Pacific region. *J Gastroenterol Hepatol*. 2004;19:958-69.
46. Cheung J, Lee TK, Teh CZ, Wang CY, Kwan WC, Yoshida EM. Cross-sectional study of hepatitis B awareness among Chinese and Southeast Asian Canadians in the Vancouver-Richmond community. *Can J Gastroenterol*. 2005;19(4):245-9.
47. Cotler SJ, Cotler S, Xie H, Luc BJ, Layden TJ, Wong SS. Characterizing hepatitis B stigma in Chinese immigrants. *J Viral Hepat*. 2012;19(2):147-52.
48. Sam JJ, Heathcote EJ, Wong DKH, Wooster DL, Shah H. Hepatitis B learning needs assessment of family medicine trainees in Canada: Results of a nationwide survey. *Can J Gastroenterol*. 2011;25(3):127-34.

# The Adverse Health Effects of Persistent Cannabis Use: Review & Recommendations for Change

Benjamin J. Tuyp<sup>a</sup>, BA

<sup>a</sup>Vancouver Fraser Medical Program 2014, UBC Faculty of Medicine, Vancouver, BC

## ABSTRACT

Cannabis is the world's most widely used illicit drug. As consumption rates increase, societies are beginning to reconsider its legal status. In order to advise patients and policymakers, clinicians must remain informed of the adverse health effects of marijuana. Established risks include respiratory disease, cardiovascular disease, cognitive impairment, psychotic illness, and motor vehicle collisions. These damages are magnified in heavy users and in those initiating consumption at an early age. This paper focuses on the well-demonstrated harms of persistent marijuana use, providing clinicians with a foundation of knowledge and a series of lower-risk usage guidelines to augment discussions on drug policy and patient risk.

**KEYWORDS:** *cannabis, harm reduction, substance-related disorders, cognition, mental illness*

More than 10% of Canadians report cannabis use in the last year, a figure that increases to one-third in the young adult population.<sup>1</sup> Public opinion on the drug's legal status is changing: 66% of Canadians are now in favour of decriminalizing or legalizing marijuana, with 40% calling for taxable distribution.<sup>2</sup> In order to participate in discussions with patients and policymakers, clinicians must remain abreast of marijuana's adverse effects on health. Medically, cannabis has demonstrated efficacy in promoting weight gain, controlling nausea, palliating peripheral neuropathy, and reducing muscle spasticity.<sup>3</sup> Recreational users describe benefits including increased relaxation, enhanced sociability, and heightened insight.<sup>4,5</sup> On the other hand, serious and permanent harms can result from marijuana exposure, especially in young-onset and heavy users.

This brief review focuses on the well-demonstrated adverse health effects of marijuana: respiratory disease, cardiovascular disease, cognitive impairment, psychotic illness, and motor vehicle collisions. A set of risk-lowering cannabis use criteria is then introduced.<sup>1</sup> At the end of this review, the reader will be able to

“ Although smoking remains the most popular method of intoxication, this requires the inhalation of tar, carbon monoxide, and carcinogenic polycyclic aromatic hydrocarbons in addition to  $\Delta 9$ -THC.

discuss the risks of marijuana use be able to offer a harm-reducing set of usage guidelines to populations intolerant of abstinence.

Cannabis users ingest delta-9-tetrahydrocannabinol ( $\Delta 9$ -THC), marijuana's active ingredient, by eating, smoking, or vaporizing the drug. Although smoking remains the most popular method of intoxication, this requires the inhalation of tar, carbon monoxide, and carcinogenic polycyclic aromatic hydrocarbons in addition to  $\Delta 9$ -THC.<sup>6</sup> As a consequence, up to one-third of marijuana smokers experience cough, wheeze, and increased sputum production.<sup>7</sup> Uncertainty remains as to whether obstructive changes in lung function—as seen in asthma, bronchitis, and emphysema—underlie this symptomatology.<sup>7</sup> At the cellular

## Correspondence

Benjamin Tuyp, bjtuy@gmail.com